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Appendix 7: Drug-Induced Pulmonary Disease

TABLE A7-1

Summary of Drug-Induced Pulmonary Disease—Presentation, Diagnosis, Causative Agents, and Management

Disease	Presentation	Key Diagnostic Components	Causative Agents	Management
Reactions Involving the Interstitium				
Interstitial pneumonitis and fibrosis	Can be acute or chronic Dyspnea, cough, clubbing, crackles	History of drug exposure Bilateral localized or diffuse opacities and reduced lung volumes on CXR "Honeycombing" on chest CT Elevated ESR with amiodarone Restrictive/normal PFTs	Amiodarone, bleomycin, gemcitabine, carmustine, cyclophosphamide, taxanes, EGFR inhibitors, dasatinib, mTORi, busulfan, sulfasalazine, methotrexate, leflunomide, phenytoin, nitrofurantoin, daptomycin	Drug discontinuation, dose reduction or interruption Corticosteroids Supplemental oxygen
Organizing pneumonia	Nonproductive cough, shortness of breath, bilateral crackles Less commonly, fever	History of drug exposure Bilateral patchy infiltrates on CXR Rarely, eosinophilia present	Amiodarone, bleomycin, minocycline, nitrofurantoin, gold, sulfasalazine, interferon alpha, carbamazepine, L-tryptophan, cocaine	Drug discontinuation Corticosteroids Supplemental oxygen
Eosinophilic pneumonia	Can be acute or chronic Dry cough, dyspnea, chest pain, fever	History of drug exposure Bilateral reticular ground-glass opacities on chest CT Acute: elevated peripheral neutrophils with high BAL	Daptomycin, mesalamine, sulfasalazine, minocycline	Drug discontinuation Corticosteroids Omalizumab Supplemental oxygen Acute: mechanical ventilation common

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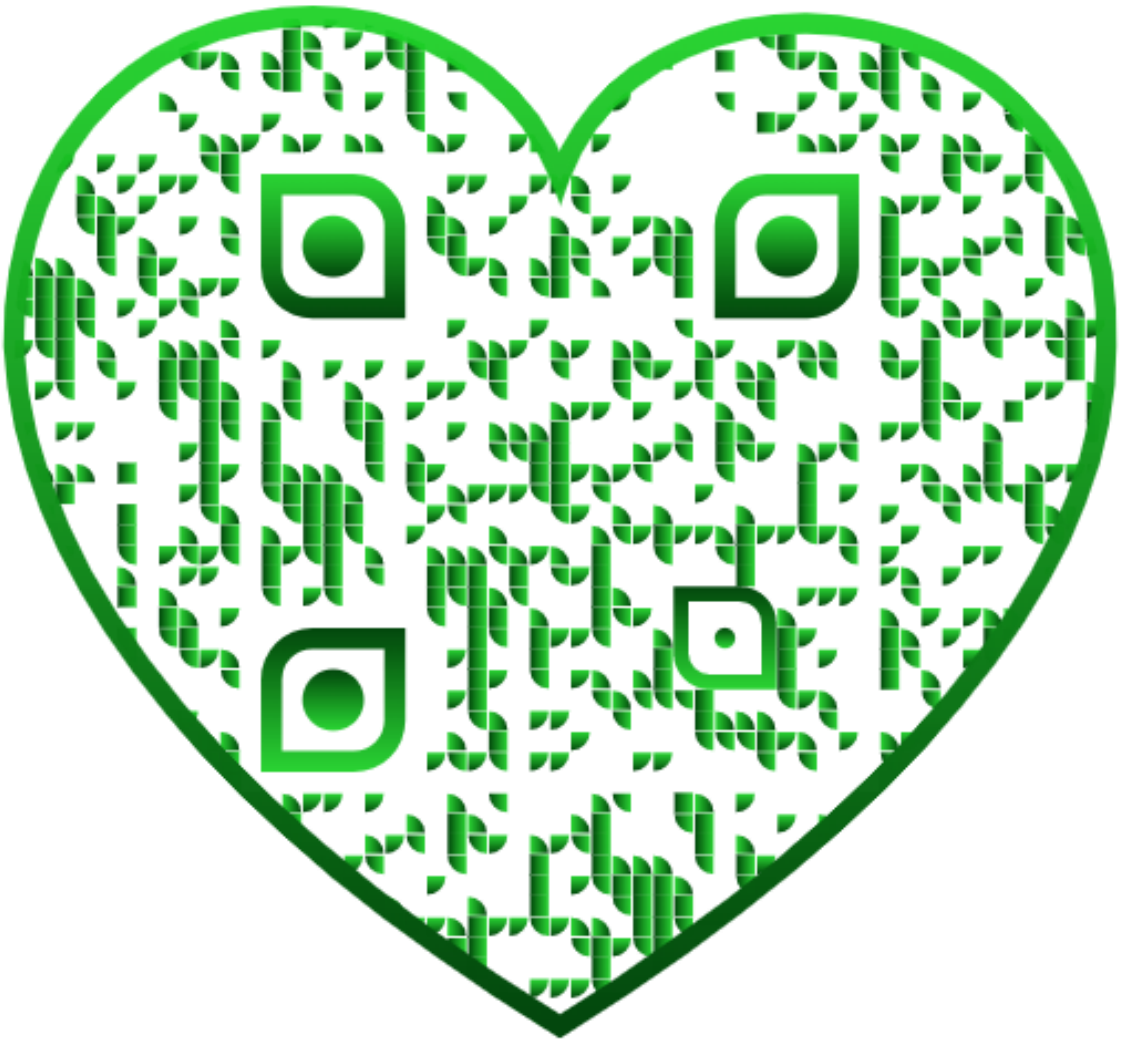

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		eosinophils Chronic: elevated peripheral eosinophils, elevated IgE, CRP, ESR		
Hypersensitivity pneumonitis	Usually, immediate Urticaria, angioedema, rhinitis, conjunctivitis, dyspnea, and bronchospasm	History of drug exposure Based on presentation	NSAIDs (dose-dependent), methotrexate, nitrofurantoin	Drug discontinuation Corticosteroids Antihistamines Supplemental oxygen
Noncardiac pulmonary edema	Dyspnea, chest discomfort, tachypnea, hypoxemia	History of drug exposure Interstitial and alveolar infiltrates Laboratory values and PFTs not helpful	Cytarabine, gemcitabine, immune globulins, interleukin, methotrexate, mitomycin muromonab-CD3, pentostatin, tretinoin, tricyclic antidepressants, aspirin (dose-dependent), methadone, morphine, oxytocin, protamine, heroin, cocaine, cytarabine, infliximab, GM-CSF, vinca alkaloids, amiodarone, nitrofurantoin, talc	Drug discontinuation Diuretics Supplemental oxygen Mechanical ventilation Role of corticosteroids is questionable
Diffuse alveolar damage	Typically acute, can be subacute Hemoptysis, cough, dyspnea, acute respiratory failure	History of drug exposure New or unexplained infiltrates on CXR Dropping hematocrit Hemorrhagic BAL	Chemotherapy, all-trans-retinoic acid, propylthiouracil, penicillin, sulfasalazine, hydralazine, leukotriene antagonists, mitomycin, amiodarone, nitrofurantoin, crack cocaine, thrombolytics, anticoagulants, antiplatelet agents, dextran 70	Drug discontinuation Reversal of coagulation Corticosteroids for chemotherapy-induced causes Supplemental oxygen
Reactions Involving the Pleura				
Non-lupus-related pleural effusion	Pleuritic chest pain, pleural effusions	History of drug exposure Pleural fluid eosinophilia (nonspecific) Elevated peripheral	Sclerotherapy agents (most common), amiodarone, minoxidil, methysergide, bromocriptine, bleomycin, mitomycin, procarbazine, methotrexate, cyclophosphamide, dasatinib	Drug discontinuation Corticosteroids Supplemental oxygen

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		eosinophils		
Lupus-related pleural effusion	Pleuritic chest pain, pleural effusions	History of drug exposure Similar to idiopathic lupus Pleural fluid: exudative, ANA higher than serum values, lupus erythematosus cells may be present	Procainamide (most common), hydralazine, chlorpromazine, isoniazid, D-penicillamine, methyldopa, quinidine	Drug discontinuation Supplemental oxygen
Reactions Without Direct Toxic Effect on the Lung Tissue				
Bronchospasm	Wheezing	History of drug exposure Based on presentation	Acetaminophen, aspirin, NSAIDs, beta-blockers, iodinated radiocontrast dye	Drug discontinuation Corticosteroids Supplemental oxygen
Cough	Can occur within hours to months Persistent dry cough, "tickle" in throat	History of drug exposure Based on presentation	ACE-inhibitors, calcium channel blockers, fentanyl, latanoprost ophthalmic	Drug discontinuation
Pulmonary arterial hypertension	Dyspnea	History of drug exposure mPAP ≥25 mm Hg at rest during RHC	Anorectic agents, amphetamines, dasatinib, selective serotonin inhibitors (risk to newborn if mother taking)	Drug discontinuation Pulmonary vasodilators
Thromboembolic disorders	Dyspnea	History of drug exposure Pulmonary embolism on chest CT	Bleomycin, cyclophosphamide, alkylating/alkylating-like agents, mitomycin, high-dose combined oral contraception, immune checkpoint inhibitors	Drug discontinuation Anticoagulation Thrombolysis Supplemental oxygen
Apnea	Hypoventilation	History of drug exposure Based on presentation	Opioids, neuromuscular blockers	Dose reduction or discontinuation of drug Naloxone (for opioids)

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Chest wall rigidity	Decreased compliance of chest wall, respiratory muscles, or laryngeal structures	History of drug exposure Based on presentation	Synthetic opioids (fentanyl, remifentanil, methadone), as well as morphine	Dose reduction or discontinuation of drug

ANA, antinuclear antibodies; BAL, bronchoalveolar lavage; CRP, c-reactive protein; CT, computerized tomography scan; CXR, chest X-ray; EGFR, epidermal growth factor receptor; ESR, erythrocyte sedimentation rate; GM-CSF, granulocyte-macrophage colony-stimulating factor; mPAP, mean pulmonary arterial pressure; mTORi, mechanistic target of rapamycin inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs; PFTs, pulmonary function tests; RHC, right heart catheterization.

TABLE A7-2

Diagnostic Criteria for the Presence of Drug-Induced Pulmonary Diseases (DIPD)

History
Known or suspected exposure to a drug known to cause DIPD
Current
Clinical and histopathological findings correlate with previous reports of DIPD
Other causes of clinical and histopathological findings can be ruled out
Future
Clinical manifestations improve after withdrawal of the drug
Clinical manifestations recur after rechallenge

(*See Chapter e51, Drug-Induced Pulmonary Diseases, authored by Margaret A. Miklich and Mojdeh Heavner, for a more detailed discussion of this topic.*)

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